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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,421	01/18/2002	John E. Sims	3086-A	6827

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EXAMINER
JIANG, DONG

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,421	SIMS ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-15* is/are pending in the application.

4a) Of the above claim(s) *2, 3 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-3 and 6-15* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's election without traverse of Group II invention, the original claims 1, 4-7 and 9-15, filed on 09 September 2004 is acknowledged.

Applicant's amendment filed on 09 September 2004 is acknowledged and entered. Following the amendment, claims 4 and 5 are canceled, and claims 1, 6, 9-12, 14 and 15 are amended.

Currently, claims 1-3 and 6-15 are pending, and claims 1, 6, 7 and 9-15 are under consideration. Accordingly, claims 2, 3 and 8, as non-elected inventions, are withdrawn from consideration.

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 and the dependent claims 6, 7 and 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a method of treating psoriasis and viral hepatitis using IL-18R antibody, does not reasonably provide enablement for claims to a method of treating renal failure due to ischemia using IL-18R antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 1 is directed to a method of treating psoriasis, renal failure due to ischemia, and viral hepatitis by administering an IL-18 antagonist, IL-18R antibody. However, the

specification merely provides examples of treatment of rheumatoid arthritis (RA) and innammatory bowel disease (IBD) with an IL-18 antagonist, and provides no guidance or working examples as to how to treat the claimed disorders, such as renal failure due to ischemia with an IL-18 antagonist. A search of the art does not reveal that an IL-18 antagonist is suitable for the treatment of renal failure due to ischemia, nor that IL-18 is involved in renal failure due to ischemia. Further, given the fact that RA and IBD are not so related ideologically or pathologically to renal failure due to ischemia, one skilled in the art would not be able to extrapolate and conclude from the success of the treatment of RA and IBD with an IL-18 antagonist that such treatment would necessarily be beneficial for patients with renal failure due to ischemia. Therefore, in the absence of any supporting evidence, it is highly unpredictable that the claimed method would be suitable for treating such a condition. As such, undue experimentation would be required prior to using the claimed invention.

Due to the large quantity of experimentation necessary to determine whether the IL-18R antibody therapy is applicable to renal failure due to ischemia, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the art, which has not established an association between IL-18 and renal failure due to ischemia and that antagonizing IL-18 might be useful therapeutically for this condition, and the breadth of the claims, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6, 9-12, 14 and 15, are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahdel-Meguid et al., US6,706,487 B1, and in view of Torigoe et al., US6,600,022 B1.

Ahdel-Meguid discloses a method for treating conditions with excess Th1 production, such as autoimmune diseases including MS, RA, IDDM, IBD and psoriasis, by administering a composition comprising an anti-IL-18 antibody (the abstract, column 3, lines 23-27, and column 14, line 65 to column 15, line 11). Additionally, Ahdel-Meguid teaches that Th1 cells, which produce proinflammatory cytokines such as IFN-γ, IL-2 and TNF-β, have been implicated in mediating many of autoimmune diseases, including MS, RA, IDDM, IBD and psoriasis, and thus, antagonism of a Th1-promoting cytokine such as IL-18 would be expected to inhibit disease development (column 1, lines 51-59), and that IL-18 is a desirable target for the development of a novel therapeutic for autoimmunity (column 2, lines 10-11). Further, Ahdel-Meguid teaches that the dose and duration of treatment relates to the relative duration of the antibody in the human circulation, and can be adjusted by one of skill in the art depending upon the condition being treated and the general health of the patient (column 15, lines 21-25).

Ahdel-Meguid does not teach a method for treating said diseases/conditions such as psoriasis with an anti-IL-18R antibody.

Torigoe teaches a monoclonal antibody for human IL-18R, which fragments (SEQ ID NO:3-10) are 100% identical to that of SEQ ID NO:4 of the present invention (see appended computer printout of sequence alignment). Additionally, Torigoe teaches that the antibody was confirmed to efficiently inhibit the physiological functions of IL-18 (column 2, lines 34-39, and Example 3-2(c)), and thus efficacious in treating various diseases to which IL-18 would be directly or indirectly related such as inflammation and autoimmune diseases (column 9, lines 40-49). Further, Torigoe teaches humanized antibodies for IL-18R (column 8, the second paragraph).

Therefore, with respect to claims 1 and 6, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat a patient with an autoimmune disease such as psoriasis with an IL-18 inhibitor as indicated by Ahdel-Meguid, such as a humanized antibody for IL-18R as taught by Torigoe. The person of ordinary skill in the art would have been motivated to do so for disease treatment, and reasonably would have expected success because Ahdel-Meguid has indicated the involvement of IL-18 in autoimmune diseases such as psoriasis, and Torigoe has confirmed the inhibitory effect of the anti-IL-18R antibody on the physiological functions of IL-18.

With respect to the limitation of the administration duration and method in 9 and 10, given the state of the art at the time the present invention was filed, as indicated by Ahdel-Meguid, a person skilled in the art would readily be able to determine such based upon the condition being treated, the general health of the patient, and the most commonly used administering method in the field. Further, given the fact that the limitation of "one or more times per week" in the present claim represents a broad range of possible duration, an artisan would have to determine a specific duration suitable for each specific condition being treated within the scope of sound medical judgment.

With respect to claims 11, 12, 14 and 15, wherein the antibody is administered in combination with one or more compounds including "antagonists of inflammatory cytokines" (claim 11), such as a TNF inhibitor, and/or an antagonist to IFN-γ (claims 12, 14 and 15), it would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat a patient with an autoimmune disease such as psoriasis with an IL-18 inhibitor as indicated by Ahdel-Meguid, such as an antibody for IL-18R as taught by Torigoe, in combination with a TNF inhibitor, and/or an antagonist to IFN-γ as TNF-β and IFN-γ are proinflammatory cytokines, and are involved in the disease development, taught by Ahdel-Meguid. The person of ordinary skill in the art would have been motivated to do so for disease treatment, and reasonably would have expected success because the proinflammatory cytokines IFN-γ and TNF-β have been implicated in mediating the disease, as taught by Ahdel-Meguid.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahdel-Meguid et al., US6,706,487 B1, and in view of Torigoe et al., US6,600,022 B1, as applied to claims 1, 6, 9-12, 14 and 15 above, and further in view of Huston et al. (Proc. Natl. Acad. Sci., 1988, 85(16):5879-83).

The teachings of Ahdel-Meguid and Torigoe are reviewed above. Neither reference teaches a single chain antibody for the IL-18R.

Huston teaches a method of constructing an anti-digoxin single chain antibody fragment, scFv (see page 5879-80, and Figure 2 of the reference), which retained the antigen binding activity and specificity of the parent antibody. As known in the art, scFv is one approach to stabilizing the Fv fragments in bacteria. The main advantages of scFv are the rapid clearance from human circulation and reduced toxic side effects (Sandhu, 1992, Critical Reviews in Biotech., 12(5/6): 437-462, especially page 450, F).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the IL-18R antibody taught by Torigoe to make a single chain antibody following the method taught by Huston, for treating a patient with an autoimmune disease such as psoriasis because of the known advantages of a single chain antibody such as reduced toxic side effects. The person of ordinary skill in the art would have been motivated to do so for disease treatment, and reasonably would have expected success because Huston has successfully demonstrated such an antibody.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahdel-Meguid et al., US6,706,487 B1, and in view of Torigoe et al., US6,600,022 B1, as applied to claims 1, 6, 9-12, 14 and 15 above, and further in view of Jacobs et al. (US5,605,690).

The teachings of Ahdel-Meguid and Torigoe are reviewed above. Neither reference teaches an TNF inhibitor of TNFR:Fc.

Jacobs teaches a TNF antagonist, a soluble TNFR:Fc fusion protein (Example 2), and a method for treating TNF-dependent inflammatory diseases by administering said TNF antagonist (Examples 4-6).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat a patient with an autoimmune disease such as psoriasis with an IL-18 inhibitor as indicated by Ahdel-Meguid, such as an antibody for IL-18R as taught by Torigoe, in combination with a TNF inhibitor such as the TNFR:Fc taught by Jacobs as TNF-β is a proinflammatory cytokine, and is involved in the disease development, taught by Ahdel-Meguid. The person of ordinary skill in the art would have been motivated to do so for disease treatment, and reasonably would have expected success because Torigoe has confirmed the inhibitory effect of the anti-IL-18R antibody on the physiological functions of IL-18, and Jacobs has demonstrated the effectiveness of the TNFR:Fc on treating a TNF-dependent inflammatory disease.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
11/18/04